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Discovery of 2-(1*H*-indazol-1-yl)-thiazole derivatives as selective EP_1 receptor antagonists for treatment of overactive bladder by core structure replacement

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ABSTRACT

We have designed a series of potent EP_1 receptor antagonists. These antagonists are a series of 2-(1*H*-indazol-1-yl)-thiazoles in which the core structure was replaced with pyrazole-phenyl groups. In preliminary conscious rat cystometry experiments, two representative candidates, **2** and **22**, increased bladder capacity. In particular, the increase using **22** was approximately 2-fold that of the baseline. More detailed profiling of this compound and further optimization of this series promises to provide a novel class of drug for treating overactive bladder (OAB).

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Overactive bladder (OAB) is defined by The International Continence Society as a 'symptom syndrome which includes urinary urgency with or without urge incontinence, urinary frequency, and nocturia'.[1] In addition, urinary incontinence is generally defined as an 'involuntary loss of urine that is objectively demonstrable and is a social or hygienic problem', and urinary urgency is generally understood as a 'state at which strong and sudden desire to urinate occurs and the urge cannot be controlled'.[2]

The causes of OAB may include a change in bladder function due to aging, cerebral hemorrhage, cerebral infarction, Parkinson's disease, a neuronal disorder such as spinal injury, lower urinary tract obstruction due to prostatic hypertrophy, and a sensitive bladder due to expression of an irritative voiding symptom caused by a hypersensitive bladder resulting from chronic interstitial cystitis. However, for most cases, the cause remains unknown.[3]

Prostaglandin E_2 (PGE_2) has been suggested as a putative stimulant of afferent nerves of the bladder via the EP_1 receptor. Consequently, EP_1 receptor antagonists are a promising strategy for treating OAB.[4] A number of companies are pursuing EP_1 receptor antagonists, but very limited information on their clinical development is available, except for AstraZeneca's ZD6416,[5] and Ono Pharmaceutical's ONO-8130[6] and ONO-8539.[7] Most recently, KYORIN Pharmaceutical Co., Ltd and Kissei Pharmaceutical Co., Ltd are currently co-evaluating their candidate in Phase I clinical trials.[8]

We previously identified 2-(pyrazolyl-1-yl)-thiazole **1** as showing good EP_1 receptor antagonist activity and selectivity.[9] We further optimized **1** and identified **2** as having high activity and good physicochemical properties.[10] However, we thought it was needed to improve the potency of this series for providing the clinical candidate. To identify new compounds with unique profiles including high potent in vivo activity, we attempted synthetic approaches different from previous strategies applied to **1**. We modified the core structure of **1** because our earlier studies suggested that a smaller structure is more suitable for EP_1 receptor affinity.

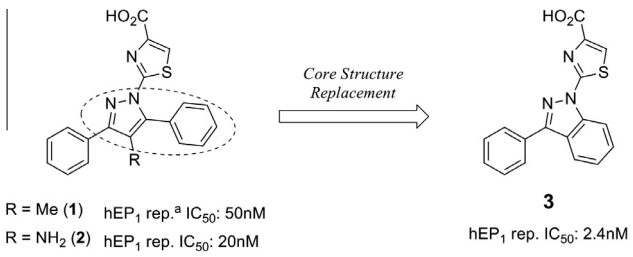

Figure 1. Replacement of core structure of **1**. (a) hEP1 rep.: 'human EP1 reporter assay'.

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Therefore, we investigated replacing the pyrazole-phenyl with a bicyclic indazole system and generated compound **3**. Compound **3** exhibited significantly increased EP_1 receptor antagonist activity (IC_{50}: 2.4 nM), confirming that we had identified a new structure with high potency (Fig. 1).

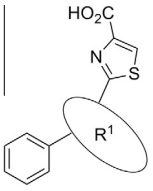
We next investigated the replacement of the pyrazole-phenyl with other bicyclic systems. Indole **4** showed high potency (IC_{50}: 4.0 nM), but was intrinsically unstable (rat CLint: 2396 mL/min/kg). Tetrahydro six-membered derivative **5** retained potency, whereas five, seven and eight membered ring compounds exhibited decreased potency. These data suggested that the six-membered moieties fit into a hydrophobic pocket. Dihydropyran **9** showed decreased potency, together with pyrazolopyridine **10**, **11** and **12**. These data suggested that the pocket accommodating the bicyclic system is unsuitable for polar groups, leading us to identify the indazole ring as the best core structure. We thus further substituted this position (Table 1).

To identify the candidate position for increasing activity, we scanned using fluorine. 4-F (**13**) showed significantly decreased activity (IC_{50}: 500 nM) whereas 5-F (**14**) was tolerated (IC_{50}: 80 nM). Since 6-F (**15**) was found to retain EP_1 receptor antagonist activity (IC_{50}: 2 nM), we focused on the 6-position on the indazole to further optimize the compound. 6-Me (**16**) exhibited increased potency (IC_{50}: 1.0 nM), and the 6-OH substitution (**17**) was tolerated (IC_{50}: 140 nM). These data were similar to that obtained during optimization of the core structure. Conversion of 6-OH (**17**) to 6-OMe (**18**) improved potency (IC_{50}: 1.1 nM) whereas conversion to 6-OEt (**19**) decreased potency (IC_{50}: 100 nM). 6-NH_2 (**20**) retained potency (IC_{50}: 19 nM), whereas there was an increase in the potency of 6-NHMe (**21**) (IC_{50}: 50 nM). Finally, 6-CF_3 (**22**) was identified as exhibiting the best EP1 activity (IC_{50}: 0.6 nM) (Table 2).

We next optimized the 3-position phenyl-group on the indazole ring. Comparison of the activity of 4-F (**23**) and 3-F (**24**) showed that the *para* position was preferred to the *meta* position. 4-Cl (**25**) showed slightly decreased activity whereas 4-MeO (**26**) retained potency. However, 4-CF_3 (**27**) exhibited significantly decreased activity, suggesting that this bulky group could not be accommodated by the ring structure of the compound. Although we speculated that a smaller group will be preferred in this part of the compound, cyclopentenyl (**28**) showed decreased activity (IC_{50}: 80 nM) and cyclohexyl (**29**) showed high potency (IC_{50}: 4 nM). These data suggested that a six-membered ring was a suitable moiety. We also evaluated other heterocyclic systems. 3-Thienyl (**30**) was tolerated, whereas 5-pyrimidyl (**31**) showed significantly decreased activity, indicating that an external position for the hydrophobic structure was preferred. Compounds containing the saturated cyclic system, 1-*N*-piperidyl (**32**) or 4-methyl-1-*N*-piperidyl (**33**), retained potency. However, both these compounds showed positive reactions in the Ames test and so were considered unsuitable due to safety concerns. Consequently, the phenyl group was chosen as the best structure for the 3-position on the indazole ring (Table 3).

Figure 2 compares the profiles of compounds **22** and **2**, which we previously reported as having good profiles.[10] Both compounds show good selectivity for the EP_1 receptor and a good profile, except for low water solubility between pH 1.2 and pH 6.8. The

Table 1
Optimization of core structure R^1



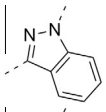
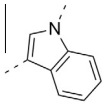
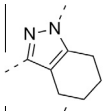
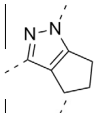
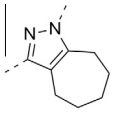
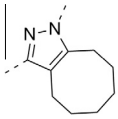
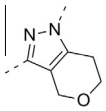
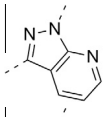
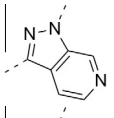
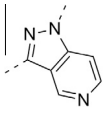
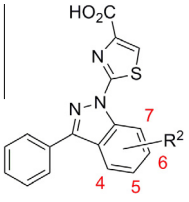
Compd	R^1	hEP_1 rep. 1 μM inhibition	hEP_1 rep. IC_{50} (nM)	rat CLint (mL/kg/min)
3			2.4	194
4			120	2396
5			16	290
6		0%		ND
7			1000	ND
8		6%		ND
9		8%		ND
10			200	65
11			39	69
12		13%		ND

Table 2
Discovery of substituted group R^2



Compd	R^2	hEP_1 rep. IC_{50} (nM)	rat CLint (mL/kg/min)
3	–H	2.4	194
13	4-F	500	280
14	5-F	80	345
15	6-F	2	337
16	6-Me	1	ND
17	6-OH	140	522
18	6-OMe	1.1	196
19	6-OEt	100	ND
20	6-NH_2	19	208
21	6-NHMe	50	ND
22	6-CF_3	0.6	186

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